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PATENT SPECIFICATION

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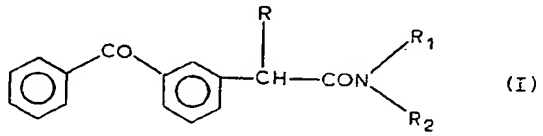
(54) AMIDE DERIVATIVES OF 3-BENZOYL-PHENYLALKANOIC ACIDS

(71) We, ANTONIO GALLARDO S.A., of Cardoner 68—74, Barcelona 12, Spain, a body corporate organised under the laws of Spain, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new amide derivatives of 3-benzoylphenylalkanoic acids which have anti-inflammatory, analgesic and antipyretic activity and are of value for the treatment *inter alia* of painful inflammatory conditions such as rheumatoid arthritis, osteoarthritis and various non-specific types of inflammatory disease affecting fibromuscular tissue. The invention also relates to pharmaceutical compositions comprising the new derivatives.

According to one aspect of our invention, we provide a compound corresponding to the general formula (I):



(I)

where R represents a hydrogen atom, lower alkyl (C_1—C_5) radical or cycloalkyl radical; R_1 represents a hydrogen atom or lower (C_1—C_5) alkyl radical; and R_2 represents a heterocyclic group having one or more heteroatoms, or R_1 and R_2 together with the adjoining nitrogen atom form 3-oxo-4,5-benzo-1,2-thiazolinyl-1,1-dioxide, or a pharmaceutically acceptable salt thereof.

The radical R in formula (I) is preferably a hydrogen atom or a methyl group. R_1 is preferably a hydrogen atom. R_2 is preferably 2-thiazolinyl, 4-methylpyridyl, 3-hydroxypyridyl, pyridyl, 1,5-dimethyl-2-phenyl-pyrazolonyl, or thiazolyl.

According to another aspect of our invention, we provide a pharmaceutical composition comprising a compound of formula (I) as defined above, together with a non-toxic pharmaceutically acceptable carrier or diluent therefor.

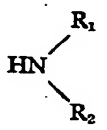
The carrier or diluent may be solid or liquid. Preferred examples are lactose, corn starch, colloidal silicon dioxide, microcrystalline cellulose, carboxymethyl starch, hydroxypropyl cellulose, magnesium stearate and *adeps solidus*.

According to a further aspect of our invention, we provide a process for preparing a compound of formula (I) as defined above, which comprises hydrolysing a 3-benzoylphenyl α-substituted acetonitrile to form the corresponding alkanoic acid, converting the acid to an active derivative, and reacting the active derivative with an amine to form the desired amide derivative of formula (I).

The compounds may be prepared from the corresponding 3-benzoylphenyl α-substituted acetonitrile by hydrolysis in aqueous mineral acids, such as sulphuric, hydrochloric or phosphoric acid or organic acids such as formic, acetic, halogen substituted acetic acids or propionic acid at temperatures in the range of from 70° to 100°C.,

when the corresponding 3-benzoylphenyl alkanoic acids are obtained. These may be converted into the acid chlorides in solvents such as benzene, toluene, chloroform or xylene with chlorinating agents such as thionyl chloride, phosphorus pentachloride or oxalylchloride at temperatures in the range of from 80° to 120°C. The acid chlorides may then be reacted with an amine of the general formula (II).

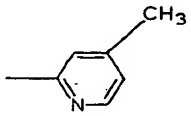
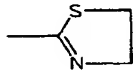
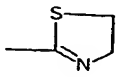
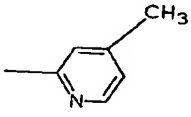
(II)



in which R_1 and R_2 have the same meaning as indicated above, in solvents such as benzene, toluene, acetone or dioxane and in the presence of a strong base such as sodium hydroxide, potassium hydroxide, triethylamine or pyridine. The reaction is controlled and maintained at room temperature initially and finally completed at 70°—90°C.

In the screening tests used to detect antiinflammatory, analgesic and antipyretic activity, some of the compounds were highly active and were shown to be intermediate in activity between the known antiinflammatory agents, phenylbutazone and indomethacin. The activity of some of the compounds is shown below:

Structure I

R	R_1	R_2	*carrag. oedema	*analgesic activity	*antipyret. activity
H	H		4	4	4
CH_3	H		5	5	5
H	H		4	4	4
CH_3	H		4	4	4
Phenylbutazone			3	1	1
Indomethacine			5	5	5

* Activity is expressed as approximate ED_{50} values (mg/kg. per os) as follows >250 = 0; 126–250 = 1; 63–125 =2; 31–62 =3; 15–30 =4, <15 =0.

Those compounds having a sufficiently basic heteratom may be used in the form of salts with organic or inorganic acids.

For the preparation of pharmaceutical compositions the active compounds may be diluted with pharmaceutically acceptable ingredients to form the compositions of this invention, the type of excipients used depending on the route of administration. Oral forms may take the form of tablets, capsules, lozenges or effervescent granules or, as liquid preparations, in the form of mixtures, elixirs, syrups and suspensions. Suppositories may be prepared using excipients known in the art for this dosage form.

The pharmaceutical formulations may contain from 25 to 300 mg. and the daily dose of the active component may vary between 20 mg. and 1000 mg. per day.

The following Examples illustrate the invention, except Examples 1 and 2 which concern the production of intermediate compounds.

Example 1.

3-benzoylphenyl acetic acid (Intermediate Compound)

A mixture of 3-benzoylphenyl acetonitrile (50 g.), water (50 ml) acetic acid (50 ml) and concentrated sulphuric acid (50 ml) was refluxed with agitation for 2 hours.

After cooling the mixture was poured into water and extracted with methylene chloride. The extract was washed with water, decolourised with charcoal and dried over sodium sulphate before evaporating the solvent. The residual solid was washed well with benzene and dried to give a yield of 32 g. m.p. 112—4°C.

Example 2.

α-(3-benzoylphenyl) propionyl chloride (Intermediate Compound)

α-(3-benzoylphenyl) propionic acid (5 g.) was dissolved in dry benzene (45 ml.), treated with thionyl chloride (2.5 ml.) and the solution was refluxed for 6 hours. The solvent was removed *in vacuo* and the residue was redissolved in benzene and evaporated to dryness. This operation was repeated several times to remove the excess of thionyl chloride. In this way, a light coloured oil was obtained (5.3 g), which was used for the following reactions.

Example 3.

2-[α-(3-benzoylphenyl) propionamide]-4-methyl pyridine

2-amino-4-methyl pyridine (8 g. 0.04 moles) and triethylamine (4 g. 0.04 moles) were dissolved in dioxane (50 ml). To this solution was added, with stirring at room temperature, over the space of 1/2 hour, α-(3-benzoylphenyl) propionyl chloride (11 g. 0.04 moles) dissolved in dioxane (20 ml). When the addition was completed, the mixture was heated at 80°C. for 2 hours. The mixture was poured into ice-water and extracted several times with methylene chloride. The extracts were washed successively with water, bicarbonate and water until the washings were neutral. The extract was dried over sodium sulphate and the solvent was evaporated to leave an oil (5.2 g). The hydrochloride was prepared by treating an ethanolic solution of the product with HCl, m.p. 180—182°C.

Example 4.

By the procedure described in Example 3, the following amides were prepared from the appropriate acid chlorides and amines:

3-(3'-benzoylphenyl acetamido)-2-thiazoline — m.p. 161—62°C.
2-(3'-benzoylphenyl acetamido)-thiazole — m.p. 168—70°C.
2-(3'-benzoylphenyl acetamido)-4-methyl pyridine — m.p. 86—88°C.
2-(3'-benzoylphenyl acetamido)-3-hydroxypyridine — m.p. 144—5°C.
2-(3'-benzoylphenyl acetamido)-3-oxo-4,5-benzo-1-2-thiazoline-1,1-dioxide — m.p, 156—57°C.
3-(3'-benzoylphenyl acetamido)-pyridine — m.p. 108—10°C.
4-(3'-benzoylphenyl acetamido)-1,5-dimethyl-2-phenyl pyrazoline — m.p. 165—7°C.
2-[α(3'-benzoylphenyl)propionamide]-thiazoline hydrochloride — m.p. 72—5°C.
2-[α(3'-benzoylphenyl)propionamide]-thiazole — m.p. 130—1°C.
4-[α(3-benzoylphenyl)propionamide]-1,5-dimethyl-2-phenyl pyrazoline hydrochloride m.p. 140—2°C.

Example 5.

10,000 capsules, each containing 20 mg. of 2-[α-(3'-benzoylphenyl)propionamide]-4-methyl pyridine hydrochloride were prepared as follows:

Formulation:

2-[α-(3'-benzoylphenyl)propionamide]-4-methyl pyridine hydrochloride	200 g.
Lactose	650 g.
Corn Starch	485 g.
Colloidal silicon oxide	15 g.

Preparation:

The 2-[α-(3'-benzoylphenyl)propionamide]-4-methyl pyridine hydrochloride was mixed with the lactose, corn starch and colloidal silicon oxide and the resulting mixture was filled into 10,000 hard gelatin capsules of an appropriate size.

Example 6.

10,000 tablets, each containing 20 mg. of 2-[α-(3'-benzoylphenyl)propionamide]-thiazole, were prepared as follows:

Formulation:

2-[α-(3'-benzoylphenyl)propionamide]-thiazole	200 g.
Lactose	1.590 g.
Microcrystalline cellulose	600 g.
Carboxy methyl starch	86 g.
Colloidal silicon oxide	10 g.
Hydroxypropylcellulose	2 g.
Magnesium stearate	12 g.

Preparation:

The finely micronized 2-[α-(3'-benzoylphenyl)propionamide]-thiazole and 2 g. of colloidal silicon oxide were granulated with the hydroxypropylcellulose dissolved in a 50:50 mixture of water and ethanol in a high speed blender-granlator. The resulting granulate was dried, passed through a 30 mesh screen and mixed with the lactose, microcrystalline cellulose, carboxy methyl starch, the rest of the colloidal silicon oxide and half of the magnesium stearate. This mixture was precompressed, passed through a 16 mesh screen, mixed with the rest of the magnesium stearate and compressed into approximately 10,000 tablets each weighing about 260 mg. using a 7 mm. die and flat bevel edge punches.

Example 7.

1000 suppositories, each containing 25 mg. of 2-[α-(3'-benzoylphenyl)propionamide]-4-methyl pyridine hydrochloride, were prepared as follows:

Formulation:

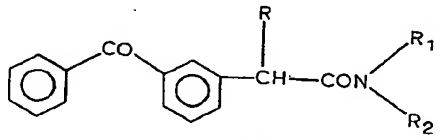
2-[α-(3'-benzoyl phenyl)propionamide]-4-methyl pyridine hydrochloride	250 g.
Adep solidus	16.250 g.

Preparation:

The *adeps solidus* was melted in an electrically heated thermostatically controlled stainless steel vat at 45°C. and the finely pulverized 2-[α-(3'-benzoylphenyl)propionamide]-4-methyl pyridine hydrochloride was added with constant stirring. The resulting suspension was poured into suppository moulds forming 1000 suppositories, each weighing approximately 1650 mg.

WHAT WE CLAIM IS:—

1. A compound corresponding to the general formula (I):



(I)

where R represents a hydrogen atom, lower alkyl (C_1—C_5) radical or cycloalkyl radical; R_1 represents a hydrogen atom or lower (C_1—C_5) alkyl radical; and R_2 represents a heterocyclic group having one or more heteroatoms, or R_1 and R_2 together with

the adjoining nitrogen atom form 3-oxo-4,5-benzo-1,2-thiazolinyl-1,1-dioxide, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R represents a hydrogen atom or a methyl group.

3. A compound as claimed in claim 1 or 2, wherein R_1 represents a hydrogen atom.

4. A compound as claimed in any of claims 1 to 3, wherein R_2 represents 2-thiazolinyl, 4-methylpyridyl, 3-hydroxypyridyl, pyridyl, 1,5-dimethyl-2-phenyl-pyrazolonyl or thiazolyl.

5. A compound as claimed in claim 1, substantially as herein described with reference to Example 3.

6. A compound as claimed in claim 1, substantially as herein described with reference to Example 4.

7. A process for preparing a compound of formula (I) as defined in claim 1, which comprises hydrolysing a 3-benzoylphenyl α-substituted acetonitrile to form the corresponding alkanoic acid, converting the acid to an active derivative, and reacting the active derivative with an amine to form the desired amide derivative of formula (I).

8. A process as claimed in claim 7, wherein the active derivative is an acid chloride.

9. A process as claimed in claim 7, substantially as herein described with reference to the specific Examples 3 or 4.

10. A compound as claimed in claim 1, when produced by a process as claimed in any of claims 7 to 9.

11. A pharmaceutical composition comprising a compound as claimed in claim 1 together with a non-toxic pharmaceutically acceptable carrier or diluent therefor.

12. A pharmaceutical composition as claimed in claim 11, substantially as herein described with reference to any of the specific Examples 5 to 7.

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